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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CELSA, BENNETT M	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 10/16/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

file copy

Office Action Summary

Application No.	Applicant(s)
09/910,461	Gluckman et al.
Examiner	**Art Unit**
Bennett Celsa	1639

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 5, 2003* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *11-46* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *11-46* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Response to Amendment

Status of the Claims

Claims 11-46 are currently pending and under consideration to the extent of the elected invention (e.g. GLY-PRO-GLU)..

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objection (s) and/or Rejection (s)

Applicant's amendment has overcome the objection of claim because of the term "introvenous".

Applicant's amendment has overcome the indefinite rejection of claims 38-41 and 43-44 for lack of antecedent basis.

Outstanding Objection (s) and/or Rejection (s)

2. Claims 11-16, 24-27, 30-31 and 36-46 are rejected under 35 U.S.C. 102(b) as anticipated by or in the alternative obvious over Sara EP0366638 (5/90) alone and further in view of the specification pages 1-2 to demonstrate inherency e.g. damage/loss of glial cells resulting from due to neural damage/injury e.g. from asphyxia/ischemia/hypoxia/stroke; and dementia disorders such as Alzheimer's addressing non-dopaminergic neurons.

The presently claimed invention is directed to a method for "protecting" (e.g. preventing) neural cell death resulting from injury or disease by administering Gly-Pro-Glu, Gly-Pro, or Pro-Glu in a "neuroprotective amount" to a mammal.

Sara discloses the administration of dipeptides (e.g. preferably gly-pro and pro-glu) and most preferably the tripeptide gly-pro-glu in pharmaceutical formulations to mammals in order to promote neuromodulation (see e.g. col. 1 lines 1-34) to treat neurodegenerative diseases and neural injury; such disease including (but not limited to) Alzheimers and neurological disorders dealing with non-dopaminergic neurons; in addition to neurotransmitter diseases (e.g. see col. 1, lines 28- top of col. 2)., and such injuries/damage including anoxic and ischemic brain damage (e.g. stroke and asphyxia); thus teaching the "the treatment of neural damage" (E.g. claim , Thus, the reference treatment of neurodenerative/neurocatabolic disease states and ischemic brain damage (e.g. stroke and asphyxia) addresses the treatment of injuries or disease which result in neural cell death.

The administration of the Sara peptides is via any "suitable route of administration"; including administration directly into the spinal fluid or systemic administration (e.g. oral or nasal). The reference further teaches systemic administration, including oral and nasal; as well as subcutaneous, intramuscular or intravenous. The reference teaching of systemic administration, including oral and nasal, would lead the skilled artisan to immediately envisage (e.g. anticipate) the small number of other conventional systemic administration routes (e.g. rectal, subcutaneous, inhalation, intraperitoneal or intramuscular), or alternatively, these systemic administration routes

would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention. The administration of the Sara peptides prior to an event "considered likely to lead to injury to glial cells or non-dopaminergic neural cells " would be immediately envisaged (e.g. anticipated) or in the alternative obvious to one of ordinary skill in the art since the reference teaching of the ability of the Sara peptides to treat "neural injury or disease states" within the scope of the presently claimed invention (e.g. asphyxia, ischemia, stroke) would envisage the use of such peptides prior to the onset of symptoms if foresees the likelihood of nerve damage resulting from a given activity.

The reference teaching of treating disease states would immediately envisage (e.g. anticipate) treatment within a reasonable time subsequent to the appearance of symptoms (e.g. up to 100 hours after CNS insult, and preferably 0.5 to 8 hours) or in the alternative, it would have been prima facie obvious to the skilled artisan to administer the reference peptide within a reasonable time following the onset of disease symptoms in order to effectively treat the disease, which would encompass up to 100 hours, and preferably 0.5 to 8 hours after disease onset.

The Sara reference teaching of the administration of "small quantities" of peptide "as low as fractions of milligrams" would anticipate the broad range of claim 55 or alternatively it would be obvious to determine an optimum range which would fall within the presently claimed broad range since the reference further motivates the skilled artisan to adjust the dosage using conventional means to achieve an optimum quantity (e.g. nanograms reaching the target site)

which would be reasonably expected to result in a concentration that would fall within the broad claimed range (see e.g col. 2, lines . 45-55).

The prior art method must inherently "prevent" neural cell death" via the same mechanism (e.g. meet mechanism limitation of present claim 56) because the reference teaches the administration of the *same peptide(s)* to the same host(s) in the *same amount (s) to treat the same diseases and/or neural injuries affecting the same neurons(glial cells/non-dopaminerci)* *See In re Best*, 195 USPQ 430,433 (CCPA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993).

3. Claims 11-17, 24-27, 30-31 and 36-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sara EP0366638 (5/90) alone (and further in view of the specification pages 1-2 to demonstrate inherency e.g. damage/loss of glial cells resulting from due to neural damage/injury e.g. from asphyxia/ischemia/hypoxia/stroke; and dementia disorders such as Alzheimer's addressing non-dopaminergic neurons) as applied to claims 11-16, 24-27, 30-31 and 36-46 above, and further in view of Sibalis US Pat. No. 5,032,109 (7/1991).

As discussed in the above anticipation/obvious rejection, hereby incorporated by reference in its entirety, Sara discloses the use of dipeptides (e.g. preferably gly-pro and pro-glu) and most preferably the tripeptide gly-pro-glu in pharmaceutical formulations for administration to mammals in the CNS and PNS to all neural tissue , cells or tissue of neural origin (e.g. see col. 2, lines 8-15) in the treatment of neurodegenerative and catabolic neuronal disease states including ischemia, Alzheimer's etc.

The Sara reference, although teaching "any suitable route" of administration including "subcutaneous, intramuscular or intravenous administration" (e.g. see Sara col. 2, especially lines 35-45), differs from the presently claimed invention (E.g. claim 17) by failing to explicitly disclose "applying an electrophoretic procedure in aid of said administration of GPE".

However, the Sibalis reference patent teaches the benefits of transdermal delivery of "polypeptides containing about three to 20 alphaamino acid units" (which would include GPE) using electrophoresis including "minimal patient discomfort"; "without irritation or reddening of the skin and without tingling or other sensations" all discomforts of which may be present via administration by other routes (e.g. injection).

Accordingly, one of ordinary skill in the art would have been motivated to utilize transdermal administration of small peptides such as Sarah's GPE via electrophoresis in order to minimize patient discomforts realized using other modes of administration.

Thus, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to apply an electrophoretic procedure as an aid in administering GPE in the Sarah method in order to obtain the benefits therefrom (e.g avoid discomforts inherent in other modes of administration e.g. injection with tingling, skin reddening or irritation; sight of the needle).

4. Claims 11-16 and 18-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sara, EP0366638 (5/90) alone (and in view of specification pages 1-2 to demonstrate inherency

e.g. damage/loss of glial cells due to neural damage/injury e.g. from asphyxia/ischemia/ hypoxia/stroke; and dementia disorders such as Alzheimer's addressing non-dopaminergic neurons) as applied to claims 11-16, 24-27, 30-31 and further in view of Gluckman et al., WO93/02695 (2/93).

As discussed in the above anticipation/obvious rejection, hereby incorporated by reference in its entirety, Sara discloses the use of dipeptides (e.g. preferably gly-pro and pro-glu) and most preferably the tripeptide gly-pro-glu in pharmaceutical formulations for administration to mammals in the CNS and PNS to all neural tissue , cells or tissue of neural origin (e.g. see col. 2, lines 8-15) in the treatment of neurodegenerative and catabolic neuronal disease states including ischemia, Altzheimer's etc.

However, the Sara reference fails to explicitly disclose:

a. the administration of the Sara peptides prior to elective procedures (e.g. cardiac bypass surgeries/brain surgeries; and via "maternal circulation" during parturition) (e.g. present claims 18 and 20-23).

b. treatment within a reasonable time subsequent to the appearance of symptoms (e.g. up to 100 hours after CNS insult, and preferably 0.5 to 8 hours) utilizing an effective amount of peptide (e.g. ; 0.1 to 1000ug per 100 gm of body weight) (claims 28-29);

c. the different types of "direct" spinal fluid administration (e.g. cerebro-ventricular injection, injection into the cerebral parenchyma or lateral cerebro ventricle shunt) (e.g. present claims 32 and 33);

d. the administration of GPE "in combination with artificial cerebrospinal fluid" (e.g. present claims 34-35).

Gluckman et al., teaches a method for the treatment or prevention of CNS damage caused by neurodegenerative disease and trauma which primarily causes damage to glia and/or other non-cholinergic cells of the CNS (e.g. See abstract; pages 1-3 and claims 1-15). For example, Gluckman et. suggest that it is desirable to prevent or reduce the amount of CNS damage which may be suffered as a result of induced cerebral asphyxia during elective surgeries e.g. as occurs during cardiac bypass surgery and child birth (e.g. "perinatal asphyxia") (see bottom of page 1 to top of page 2). The Gluckman peptide medicament(s) can be administered up to 100 hours after CNS insult, and preferably 0.5 to 8 hours after CNS insult via surgical shunt into the cerebro ventricle in amounts of 0.1 to 1000ug per 100 gm of body weight (e.g. see pages 3-4). The Gluckman peptides can be administered via "direct" spinal fluid administration (e.g. cerebro-ventricular injection, injection into the cerebral parenchyma or lateral cerebro ventricle shunt) (e.g. see pages 3-4 and 6) or optionally "in combination with artificial cerebrospinal fluid" (e.g. page 10, lines 8-15). The Gluckman administered peptide preferably comprises IGF-1 and/or analogues thereof including synthetic analogues of IGF-1 (e.g. see claims 1 and 13). It is noteworthy that the Gly-Pro-Glu peptide, as presently claimed, is derived from the N-terminal three amino acids of IGF-1 peptide..

Thus, the Gluckman reference provides conventional amounts and means of directly administering (e.g. maternal circulation when addressing fetal distress) peptides for use in treating

neurodegenerative disease, trauma and their sequelae (e.g. neural death or damage) including the desirability to prevent or reduce the amount of CNS damage which may be suffered as a result of induced cerebral asphyxia during elective surgeries e.g. as occurs during cardiac bypass surgery and child birth (e.g. "perinatal asphyxia") (see bottom of page 1 to top of page 2). .

Accordingly, one of ordinary skill in the art would be motivated to employ the same means and amounts of administration as Gluckman when employing analogous peptides for treating the same diseases and states as addressed by the Gluckman reference.

Thus, it would have been prima facie obvious to the skilled artisan at the time of applicants' invention to prevent/treat neural cell death during elective procedures (e.g. cardiac bypass surgeries; brain surgeries, cord occlusion) likely to result in loss of neurons (e.g. cell death; including glial cells) by administering Gly-pro-glu as taught by Gluckman.

Similarly, it would have been prima facie obvious to the skilled artisan to select a specific direct method of CSF administration (e.g. cerebroventricular injection) as taught by Gluckman for administration of the Gly-Pro-Glu Sara peptide; and further administer the therapeutic peptide with artificial CSF as taught by Gluckman.

Additionally it would have been prima facie obvious to the skilled artisan to administer the Sara peptide upon a reasonable time following CNS symptoms (e.g. up to 100 hours, preferably 0.5 to 8 hours) in effective amounts (e.g. 0.1 to 1000ug per 100 gm of body weight) as taught by Gluckman.

Discussion

Applicant's amendment and arguments directed to the above anticipation and obviousness rejections were considered but deemed nonpersuasive for the following reasons.

Applicant argues that the term "addresses" recited in the above rejection is unclear as to whether "addresses" "was intended to mean anticipates".

As pointed in the rejection, above the phrase:" the reference treatment of neurodenerative/neurocatabolic disease states and ischemic brain damage (e.g. stroke and asphyxia) *addresses* the treatment of injuries or disease which result in neural cell death"; is to be interpreted in the context of the preceding rejection paragraph as a reference teaching of the treatment of injuries or diseases which result in neural cell death commensurate in scope to the presently claimed invention.

Applicant further argues that to " that altering neurotransmitter release induced by cellular depolarization does not necessarily include treating 'injuries or disease which results in neural cell death'. "

Applicant's argument was considered but deemed nonpersuasive for the following reasons.

Applicant's reference to mechanism (altering neurotransmitter release induced by cellular depolarization) is not responsive to the reference teaching directed to the "treatment" (e.g. protecting) of injuries or diseases within the scope of the presently claimed invention using

peptides (GPE, gly-pro, pro-glu), and amounts (e.g. neuroprotective) w/n the claimed scope; irrespective of mechanism.

Applicant argue that "the discovery of a new effect or new use of a known composition results in a new 'conception' and thus a new 'invention' that is not necessarily unpatentable".

Applicant's argument was not found convincing since, even assuming arguendo that the prior art failed to disclose or suggest a "latent" or "inherent" property present in a compound/composition utilized in the method, the case law recognizes time and again that "mere recognition of latent properties in the prior art does not render patentable an otherwise known invention". See In re Wiseman, 596 F.2d. 1019, 201 USPQ 658 (CCPA 1979). For granting a patent on the discovery of an unknown but inherent function "would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. See 201 USPQ at 661; In re Baxter, 952 F.2d 388, 21 USPQ2d 1281 (Fed. Cir. 1991).

Applicant further argues that:

a. "neuromodulator" (e.g the Sara mechanism) differs definitionally from "neuroprotective" (e.g. the mechanism currently claimed); and

b. The Sara reference "neuromodulation" [e.g. interpreted using subsequent Sara reference article(s)] is directed to neurotransmission whereas "neuroprotective" is used by applicant to "refer to an ability to promote growth or survival of neurons or other cells".

c. There is no teaching that "both increasing and decreasing neurotransmitter release are necessarily linked to 'protecting glial cells or non-dopaminergic neural cells in a mammal against death from neural injury or disease'."

Applicant's arguments were considered but deemed nonpersuasive since, as pointed out in the rejection above, the Sara reference teaches the administration of the *same peptide(s)* to the same host(s) in the *same amount (s) to treat the same diseases and/or neural injuries affecting the same neurons(glial cells/non-dopaminerci) and thus inherently anticipates applicant's inherent resulting mechanism. See In re Best*, 195 USPQ 430,433 (CCPA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993)

Applicant further argues that the Sara reference is nonenabling regarding "potential uses of GPE to treat dementias" both with respect to effectuating neuromodulation (e.g. Sara's asserted mechanism) or neuroprotection (e.g. applicant's asserted/claimed mechanism) citing the lack of in vitro/in vivo experiments regarding "neuroprotection"(applicant's mechanism) and no in vivo experiments in which GPE was used or long-term studies of any GPE effects.

Applicant's argument was considered but deemed nonpersuasive for the following reasons.

Initially, it is noted that there is a much lower legal threshold regarding enablement of a reference , as compared to a patent application. Secondly, applicant's argument regarding the Sara reference's failure to tailor in vitro/in vivo experiment(s) directed to their purported neuroprotection is not persuasive where the reference method necessarily inherently performs

applicant's proposed mechanism . Thirdly, applicant does not question enablement with regard to making but only with respect to use. With regard to use, the Sara reference clearly teaches how to make and administer pharmaceutical compositions to treat diseases/disorders within the scope of the presently claimed invention. Additionally, the Sara reference further provides examples regarding the making of these peptides (e.g. Example 1) and three examples directed to in vitro use of the resulting peptides to "modulate" neural activity. Applicant has provided no evidence whatsoever why the *Sara reference is a non-enabling reference* by its failure to provide in vivo evidence. Accordingly, the reference is enabling absent evidence to the contrary.

Applicant argues that without some form of linking of "neuromodulation" to "neuroprotection" (assertedly not present in the Sara reference or subsequent Sara references) the Examiner has failed to provide evidence that inherency is absolutely certain and not merely a probability or possibility.

Again applicant's argument was considered but deemed not persuasive since case law has firmly established that a (preamble) limitation not explicitly taught by a reference, nevertheless is inherently taught by the reference where the reference teaches all of the method steps. *See In re Best*, 195 USPQ 430,433 (CCPA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993); *Integra LifeSciences I Ltd. V. Merck KgaA* (DC Scalif: Feb. 1999) 50 USPQ2d 1846 (subsequent "discovery" of administered peptide property in claimed method preamble was inherent in reference teaching where "manipulative steps" regarding same peptide are similar, if

not identical) . Accordingly, since the Sara reference teaches method steps within the scope of the presently claimed invention, applicant's preamble limitaion MUST (not may) inherently occur.

Regarding, obviousness applicant argues that a subsequent Sara article (Annals of NY academy of Science pp 183-191 (1991), referred to as Sara 2) teaches away ("Extensive in vivo studies have not revealed any growth-promoting activity of GPE ...") from Applicant's claims and thus "at the time of publication of Sara 2, the first inventor of Sara 1 (the Sara EP reference in the above rejections) could not have a reasonable belief that GPE could be a growth modulator; and thus there would be neither a motive to try nor a reasonable expectation of success at achieving the Applicant's invention. Applicant further cites a second subsequent Sara article (e.g Sara 3) as probative of the Sara EP reference reliance on a paticular mechanism (E.g. neuromodulator regulating neurotransmission). In short applicant argues that a Sara teaching of neuromodulation is not equivalent to neuroprotection as presently claimed.

This argument was considered but deemed nonpersuasive.

Initially, the relevance of an asserted teaching away which is NOT found in the Sara EP reference recited in the rejection but in a different reference is tenuous at bestt. Additionally, the relevance of Sara 2 and 3 is dubious at best; when these references are not being relied upon in the above rejection.

Secondly, regarding the Sara 2 reference, the Examiner questions whether "growth promoting" as referred to in the above cited phrase and neuroprotection (as presently claimed) are necessarily biologically related.

Thirdly, where the reference method teaching inherently produces applicant's claimed preamble mechanism limitation, there is no need to modify the reference method since the method already inherently meets applicant's claim limitation. The Sara reference teaching of the method steps inherently produces neuroprotection regardless of whether Sara's intent was neuromodulation or otherwise.

Applicant further argues that neither the Sibalis nor Gluckman reference teach neuroprotection properties of the presently claimed compounds.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the present instance it is pointed out in the rejection above that the Sara EP reference teaches a method which inherently results in neuroprotection as presently claimed.

Applicant argues that the Examiner has engaged in hindsight reconstruction regarding the neuroprotective properties of GPE. This argument is not persuasive since the Sara EP reference teaches the presently claimed method with the neuroprotective property of GPE being inherent to the Sara reference method.

Accordingly, the above rejections are hereby maintained.

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

General information regarding further correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew J. Wang (art unit 1639), can be reached at (703)306-3217.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bennett Celsa (art unit 1639)
October 14, 2003

BENNETT CELSA
PRIMARY EXAMINER